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Studies in Children Exposed to Low Levels of Lead

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16. ABSTRACT

Two separate studies were conducted with the overall abjective of examining the impact of lead at low dose on the neuropsychological function of children.

In the first study, a sample of children identified as having elevated lead levels in the dentine of shed deciduous teeth (N = 19) were compared to children with low dentine lead (N = 22) on electroencephalograms and a panel of 8 auditory and speech processing tasks.

Quantitative electroencephalograms were obtained from 20 sites under 4 conditions in these subjects. The spectrum from 0.5 - 32 Hz was examined; four bands were studied (alpha, beta delta, and theta) under four conditions. Of the 320 comparisons, 10 differed at P - 0.025 or less (Wilcoxin-Mann, Whitney two sample test). These 10 features, nine behavioral measures previously obtained, and maternal I.Q. were then submitted to multivariate analysis. A stepwise linear discriminate function analysis showed that adding the EEG to behavioral analysis in the model increased to discriminating power from P = 0.015 to P = 0.001.

The most useful diagnostic features were EEG slowing (delta) over the parietal cortex and decreased full scale I.Q.

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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, non-ionizing radiation, environmental carcinogenesis and the toxicology of pesticides as well as other chemical pollutants. The Laboratory participates in the development and revision of air quality criterial documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is primarily responsible for providing the health basis for non-ionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

The study described in this report was conducted under our program to determine the health implications of children exposed to low levels of lead.

F. G. Hueter, Ph.D.
Director
Health Effects Research Laboratory

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Two separate studies were conducted with the overall objective of examining the impact of lead at low dose on the neuropsychological function of children.

In the first study, a sample of children identified as having elevated lead levels in the dentine of shed deciduous teeth (N = 19) were compared to children with low dentine lead (N = 22) on electroencephalograms and a panel of 8 auditory and speech processing tasks.

Quantitative electroencephalograms were obtained from 20 sites under 4 conditions in these subjects. The spectrum from 0.5 - 32 Hz was examined; four bands were studied (alpha, beta, delta, and theta) under four conditions. Of the 320 comparisons, 10 differed at P - 0.025 or less (Wilcoxin-Mann, Whitney two sample test). These 10 features, nine behavioral measures previously obtained, and maternal I.Q. were then submitted to multivariate analysis. A stepwise linear discrimant function analysis showed that adding the EEG to behavioral analysis in the model increased the discriminating power from P = 0.015 to P = 0.001.

The most useful diagnostic features were EEG slowing (delta) over the parietal cortex and decreased full scale I.Q.

Of the 8 speech and auditory outcomes studied, significant differences favoring the low lead group were found on three measures of auditory processing: (1) Goldman-Fristoe-Woodcock Auditory Selective Attention Test, (2) Staggered Spondaic Word Test (Left noncompeting), (3) Speech Discrimination.

This report was submitted in fulfillment of Contract No. 68-02-2217 by the Children's Hospital Medical Center, Boston, Mass. under sponsorship of the U.S. Environmental Protection Agency.

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PREFACE

Concern over the health effects from exposure to lead has shifted in recent years from those obvious impairments which follow high dose exposure to those changes in the adaptation of the host which, while they may be less dramatic and are often missed, may have important, if difficult to identify, long-term consequences.

A number of biochemical alterations have been recently demonstrated in humans which appear to have virtually no threshold for lead (1, 2, 3). Considerable controversy has been raised as to whether these biochemical changes can be considered adverse health effects. Any decrease in the ability of the host to process psychological stimuli clearly compromises the organism's ability to deal adaptively with a changing environment. A change of this nature would, therefore, meet any reasonable definition of an adverse health effect.

Because young organisms appear to be more susceptible to lead, and because childrens' exposure to lead is widespread, the study of the neuropathological consequences of lead in children has become an area of intense study. In 1979, the Lead Exposure Program at the Boston Children's Hospital Medical Center demonstrated cognitive and behavioral changes in children who were dose-related to lead. The changes were found in three general areas: verbal intelligence, speech and auditory processing, and attentional performance. It seemed important to determine whether these alterations were accompanied by parallel alterations in the electrical activity of the brain, and whether the auditory and language processing could be better defined. Another Massachusetts community reported as long as 150 years ago to have a

problem with lead, provided a simultaneous opportunity to examine the classroom behavior of a different sample of children in relation to their lead exposure in more depth than previous studies.

The studies reported here are part of the ongoing activities of the Lead Exposure Program, Children's Hospital Medical Center, whose goal is to contribute to the comprehensive understanding of lead's impact on man.

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ACKNOWLEDGMENTS

The electroencephalograms in this study were obtained in the Seizure Clinic, Children's Hospital Medical Center, and analyzed by Drs. James Burchfield, Frank Duffy and Peter Bartels. The speech and hearing battery was administered and scored by Drs. Martha Lyle and Sylvia Topp. Family histories and psychological data in the Lowell, Massachusetts, sample were collected by Elise Martin. Biostatistical analyses were done by Robert Stiratelli.

The cooperation of the Department of Schools, Chelsea, Somerville, and Lowell, Massachusetts, the principals, nurses and teachers is gratefully acknowledged.

Dr. Alan Leviton, Director, Division of Neuroepidemiology, Children's Hospital Medical Center was an essential contributor to the design of these studies.

INTRODUCTION

While the toxicity of lead at high dose is widely acknowledged, considerable controversy exists as to whether lesser doses produce adverse health effects. Lead is known to inhibit certain enzyme systems at extremely low concentrations. Among those most sensitive are D-aminolevulinic acid dehydrase (1), adenyl cyclase (2), and ferrochelatase (3). It is not, however, universally accepted that these biochemical changes and others represent adverse health effects.

For the purposes of the investigations described below, an adverse health effect is defined as "an alteration in the functioning of an organism which diminishes its ability to adapt to a changing environment. As a result, the organism's longevity, vigor, or reproductive capacity is reduced." In a changing environment, the ability to register change and then make decisions based upon the data is essential to survival. The organ in which these executive functions primarily reside is the central nervous system. The organizing principal of these investigations is that the child's CNS is a candidate site for the early expression of adverse effects of lead exposure. The Lead Exposure Program at Children's Hospital Medical Center has focused on CNS performance. Earlier studies by the group (4) had reported that children thought to be undamaged by lead, but who had elevated dentine levels, were less able on a number of measures of CNS function when compared to controls. Among the performances which appeared sensitive to lead were verbal intelligence, auditory and speech processing, attention and classroom behavior (4).

This study examines the electrophysiology of the CNS of a subsample of high and low lead subjects, and also compares them on a number of other measures of auditory and speech processing. A separate sample of children from another city were evaluated by teacher ratings, family history, and their dentine lead levels measured. This offered an opportunity, not only to replicate our previous observations, but to evaluate the effects of lead on classroom performance while controlling more completely for other covariates which could be confounding.

CONCLUSIONS

Study I

Alterations in neuropsychologic function were demonstrated in electroencephalograms of asymptomatic children with elevated body lead burdens. These changes tended to be located in midline brain structures. The addition of EEG analysis to a battery of psychologic outcomes sharpened diagnostic precision remarkably.

Statistically significant decrease in function was found on three of nineteen speech processing ou-comes. Outcomes tended to favor low lead subjects generally. The relatively small sample size may be responsible for the failure of certain outcomes to reach statistical significance.

Study II

Teachers' Behavioral Ratings as a Function of Lead Burden.

The proportion of negative teachers' reports of classroom behavior tended to increase with increasing dentine lead concentrations. The items most sensitive to lead were distractibility, disorganization, ability to follow a sequence of directions, and overall classroom functioning.

After data reduction by cluster analysis, the cluster containing the items "distractible" and "disorganized" was found most sensitive to lead exposure. The impact of lead was evaluated by stepwise multiple logistic regression. A significant ($p = 0.013$) lead effect was found, controlling for major covariates. This study replicated in part a previous investigation from this laboratory which show that teachers' assessment of classroom behavior are sensitive to lead exposure (4). It goes further than that study by controlling for a number of covariates that could be related to outcome. The ability of

the child to inhibit irrelevant stimuli is critical to the task of academic learning. The item "distractible" which evaluates that ability is consistently sensitive to lead exposure. It is reasonable to expect that this deficit is related to the impaired performance on speech processing measured here.

RECOMMENDATIONS

These studies add to the weight of those which report lead effects at low dose, and demonstrate that the threshold for appearance of adverse behavioral effects is a function of the sensitivity of the methods brought to bear on measuring outcome.

The findings of alterations in EEG, speech processing, and classroom behavior in samples clinically assumed to be free of frank toxicity supports the prudence and hygienic utility of reducing lead in the environment available to children.

Studies of lead effects in children should attend to those behaviors which are expressions of the organism's ability to focus attention.

METHODS OF PROCEDURE

Study I: EEG and Speech and Auditory Processing in Children Exposed to Low Level Lead.

Study Sample: A subsample of children selected for our previous study was chosen for EEG and speech and hearing evaluation. The 3,329 children attending first and second grades in the period between 1975 and 1978 in Chelsea and Somerville, Massachusetts, made up the population sampled. The children attended 19 public schools, and came from 105 classrooms. Children were asked to submit their shed teeth to the teacher, who then verified and recorded the presence of an appropriate fresh socket.

Classification of Exposure: Children were classified according to the concentration of lead in dentine. A 1mm sagittal slice was taken from each donor's tooth, dentine chiseled out, the tooth dried, weighed and then digested in perchloric-nitric acid. Lead was measured by anodic stripping voltammetry (5).

The distribution of dentine lead levels (N = 3321 teeth) was log normal (median 12.0 ppm). Samples were analyzed in replicate, employing either a second tooth or the opposite slice of the first tooth. Agreement between replicate samples was required or the candidate subject was excluded from further analysis. To be classified as high lead, the mean of the samples was required to be $\geq$ 20 ppm. To be classified as low lead, the mean of the samples was required to be $<$ 10 ppm. The extremes of the distribution were selected for sampling because it was felt that any effect would most clearly be demonstrated by this contrast.

Selection of Children for Neuropsychological Evaluation: After their lead status had been determined, children were admitted to the study if they met

met the following criteria:

1. English was the primary home language.
2. They were full term births.
3. They had not suffered noteworthy head injury.
4. They were discharged after birth at the same time as their mothers.

Examination of the distribution of dentine lead levels and teachers' behavioral ratings included and excluded groups which demonstrated that no selection bias was imposed in this process. The sample of children then accepted for neuropsychological data analyses numbered 158 (low = 100, high = 58). A large number of covariates (39) were measured. The subjects received a 4-hour neuropsychological battery, administered in fixed order. Each child was examined singly; the psychometricians were blind to the child's lead status. A summary of the neuropsychological data analysis is presented in the appendix.

Teacher's Behavioral Rating: The teacher of every child who gave a tooth was asked to fill out an 11-item forced-choice behavioral rating scale scoring the child as "yes" or "no" on the following questions:

1. Is this child easily distracted during his/her work?
2. Can (s)he persist with a task for a reasonable amount of time?
3. Can this child work independently and complete assigned tasks with minimal assistance?
4. Is his/her approach to tasks disorganized (constantly misplacing pencils, books, etc.)?
5. Do you consider this child hyperactive?
6. Is (s)he over-excitable and impulsive?

7. Is (s)he easily frustrated by difficulties?

8. Is (s)he a daydreamer?

9. Can (s)he follow simple directions?

10. Can (s)he follow a sequence of directions?

11. In general, is this child functioning as well as other children his/her own age in the classroom?

These questions were extracted from a questionnaire developed at the Harvard Graduate School of Education. The instrument's reliability was evaluated by Miss Margaret Guild as part of her Ed.D. thesis requirement. Inter-observer agreement on the 11 items was in the range of .640 to .786. Intra-observer reliability was in the range of .801 to .905.

The EEG Speech Sub-sample: From the 158 children evaluated neuropsychologically, 19 high lead and 22 low lead subjects were selected at random and invited to return to the laboratory. No refusals were encountered. In most instances, children first were evaluated in the speech and hearing clinic and then were taken to the EEG clinic.

Electroencephalographic (EEG) Evaluation: Twenty-two low lead and 19 high lead subjects had electroencephalographic evaluations. All subjects were studied in a standard EEG laboratory. Twenty Grass gold cup electrodes were applied to the scalp according to the International 10-20 System (Figure 1). Recording of brain electrical activity was done in the "monopolar" mode using linked electrodes on the two earlobes as a reference. Signals were amplified via a Grass Model 78 polygraph, charted on polygraph paper as for a standard EEG, and recorded on a 28 channel FM Honeywell 5600E tape recorder for subsequent off-line analysis. Spectral analysis was performed on the raw EEG from each electrode via the Fast Fourier Transform (FFT) technique on a PDP-12 computer (Digital Equipment Corporation). Spectral analysis and file handling were done under the SIGSYS-12 biomedical data analysis system (Agrippa Data Systems).

Epochs of spontaneous EEG activity were recorded from each subject under 4 standard conditions: (1) relaxed, alert with eyes open (EO); (2) same, but with eyes closed (ECP);(3) during 3 minutes of hyperventilation (HV); and (4) post-hyperventilation (PHV).

Raw EEG data recorded in each of the above conditions were bandpass filtered between 0.5 and 35 Hz and analog-to-digital converted as a series of 50 2-second segments. FFT analysis was individually performed on each 2-second segment and the ensemble of 50 segments was averaged to yield a final spectrum representing 110 seconds of EEG. The final spectrum covered the frequency range of 0-64 Hz, but only the 0.5-32 Hz range was subsequently analyzed. Each average spectrum was divided into the 4 classical EEG frequency bands: delta (0.5-3.5 Hz), theta (4.0-7.5Hz), alpha (8-12 Hz), and beta (12.5-31.5 Hz). Spectral energy was summed within each of these bands and expressed as a percentage of the total spectral energy over the full frequency range 0.5-32 Hz. Prior to statistical analysis these percentages were subjected to inverse sine transformation.

In summary, the EEG data set for each subject consisted of 320 values: percent spectral energy in 4 frequency bands, recorded from 20 scalp electrode positions, under 4 conditions.

Psychologic Data: For use in multivariate statistical analysis, subjects' scores on psychologic performance tests were obtained from the data of Needleman et al.[4] Nine measures were chosen as having potentially high discriminating value based upon their showing significant differences between high and low lead populations. These were as follows: (1) Full-scale I.Q., (2) Verbal I.Q., (3) Performance I.Q., (4) Seashore Rhythm Test, (5) Sentence Repetition Test, (6) Reaction time under varying intervals of delay, Block 2 (tested at 12 sec), (7) Reaction time, Block 3 (12 sec), (8) Reaction time, Block 4 (3 sec), and (9) Token Test. Parental I.Q., a control variable was also entered into the

model.

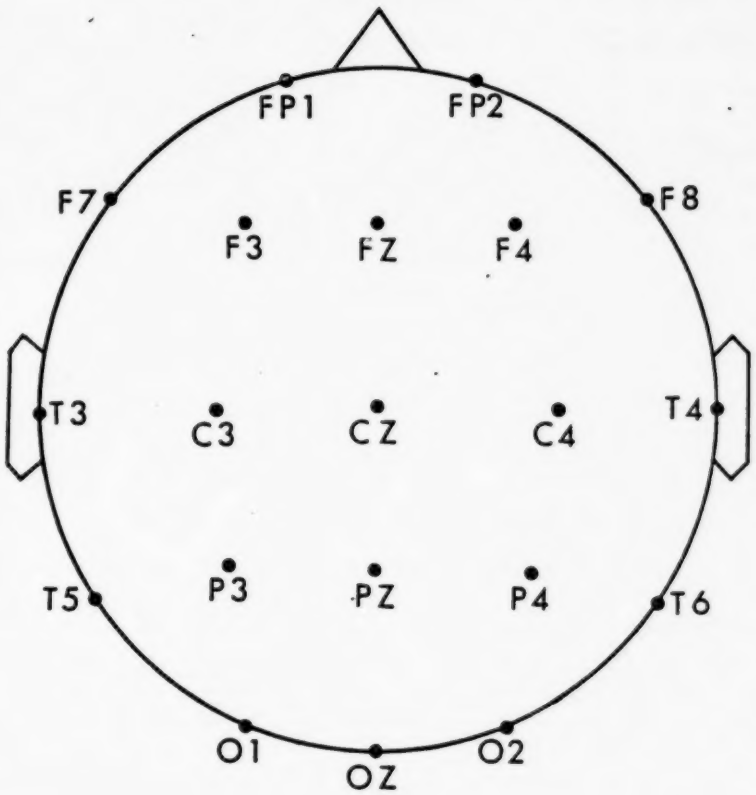
Data Analysis: The overall goal of data analysis was twofold. First, we wanted to determine whether the high and low lead populations differed significantly on any of the recorded EEG measures. To examine this we calculated population means and standard deviations of the high and low groups respectively for each of the 320 derived spectral values. Significance of group separation for homologus pairs of variables was tested by Student's t-test and by the non-parametric Wilcoxin-Mann-Whitney two-sample rank test.

The second goal was to determine the power of EEG and psychologic variables to discriminate between high and low lead subjects. To this end, multivariate analysis and non-parametric pattern recognition techniques were performed on a PDP-11/45 computer using the TICAS system of statistical programs.(5) This comprehensive system was originally developed for the automatic recognition of cancer cells based upon morphological features of their microscopically displayed images (TICAS = Taxonomic Intracellular Analytic System). However, its statistical evaluation programs are not problem specific; they can be applied to any set of descriptive features, in this case, EEG and psychologic measures.

Multivariate statistical analysis proceeded in a sequential manner as follows:

Reduction of the Dimensions of the Data Set: Statistical theory specifies a limit to the number of features per subject which can be used to demonstrate group differences or to develop classification rules to diagnose a subject as belonging to one group or another. If this limit is exceeded, the analysis becomes excessively individualized to the immediate data set and consequently does not do well on prospective tests of repeated measure on subsequent data sets. As a rough approximation, this limiting number is derived by dividing

Figure 1: Electrode placements according to the International 10-20 System.



the number of subjects in the smallest group by 3. In the present case, this = 19/3 = 6 I/3. Therefore, the initial task was to reduce the number of features from 330 (320 EEG and 10 psychologic) to 6 or less.

Data reduction was done in two steps. First, an initial screening of features was done based upon the results of univariate analysis. Those variables which did not reach a high level of significance with Student's t-test or the Wilcoxin-Mann-Whitney two sample rank test ($p \leq 0.05$) were excluded from further analysis. Next, the remaining features were subjected to Merit Value analysis. The Merit Value as formed by TICAS is a relative measure of a feature's ability to distinguish between the two populations. It is derived as the average of three independent factors. The first two factors are measures of the degree to which a given variable separates two populations. One is d-prime, the measure of "detectability" calculated from the receiver operating characteristic (ROC) curve. [6] The value of this statistic ranges from 0 (no detectability of group separation) to 0.5 (complete detectability of group separation). The other factor is the "ambiguity" value based upon the ambiguity function of Genchi and Mori.[7] A feature which totally separates two populations has an ambiguity value of 0. On the other hand, exact overlap of the populations yields the maximum ambiguity value of 1. The final factor contributing to the Merit Value is a measure of the correlation of a given feature with the other features under consideration. This was calculated as the average of the correlation coefficients between a given feature and each of the other features. The average correlation was used to detect the presence of redundant features.

Calculation of the Merit Value for a given variable was as follows:

$$\text{Merit Value} = \frac{2\,(\text{d-prime}) + (1\text{-ambiguity value}) + (1\text{-average correlation coefficient})}{3}$$

Merit Value, therefore, ranges from 0 to 1. The higher a variable's Merit Value, the better its potential usefulness for demonstrating group separation or for developing rules to classify subjects into one of two populations.

Features with high Merit Value possess a combination of high detectability, low ambiguity and low correlation with other variables.

Tests of Separation of High and Low Lead Populations and Retrospective Classification of Subjects: The features with the best Merit Value scores were submitted to direct and stepwise discriminant analyses to assess the collective ability of these features to separate high and low lead groups. The significance of group separation was tested by Wilks' lambda and the Mahalanobis distance between group centroids.[8] The former statistic may be considered as a multivariate analog of the variance ratio (F) test; therefore, an approximation of the F-statistic was calculated using the technique of Rao.[8] For stepwise discriminant analysis, retrospective classification of subjects was carried out by the Bayes classification procedure using the linear discriminant function.

Prospective Classification of Subjects: Prospective classification was carried out using the non-parametric, supervised learning programs of the TICAS. These algorithms develop classification rules for assigning subjects to one of two populations by the sequential determination of decision boundaries along the feature axes within multivariate feature space. The technique is non-parametric because subjects are arrayed along each axis by rank, rather than by absolute value of a given variable. Thus, each subject is represented by a vector whose elements are the relative rank the subject occupies within the sample population for each variable.

The classification rules are developed on a "training set" of subjects whose membership in one of the two populations is known. The procedure involves examining subjects in rank order along a given feature axis. Sampling continues as long as all subjects belong to the same population; however, as soon as the first subject of the other population is encountered, sampling stops and a

decision boundary is established. The sampled subjects of the first population are then removed and sampling proceeds in the same way with the remaining subjects on another feature axis. This continues until all subjects of one population have been removed or until the end ranks of each axis contain subjects of the other population.

Successive runs of this procedure are carried out and the order of feature selection is varied based upon previous outcomes in terms of classification success and efficiency. This is repeated until the optimum set of classification rules is developed. This procedure differs from parametric discriminant techniques in that it selects features according to their ability to classify subjects correctly from the *remaining* subset of as yet unclassified subjects. Thus, it may select features which are not weighed highly by parametric selection methods, which always consider a feature's usefulness in classifying subjects from the full sample.

Where a significant separation exists between the centroids of the two populations in multivariate space, a set of classification rules can usually be developed which will classify subjects of the training set with nearly 100% accuracy. Therefore, the true test of the diagnostic power of the classification rules, is to prospectively evaluate them on a "test set" of subjects who were not part of the original training set. Ideally, for this purpose one would like to divide the study population into separate training and test sets. In the present case, however, the population was not large enough to allow this. Instead, we established test sets by the "jackknifing" or "leaving one out" procedure.[9] Here, diagnostic classification rules were developed on a training set of 37 of our 41 subjects and tested on a test set of the remaining 4 subjects who had not been used for development of the classification rules.

This was repeated 11 times with a different set of 4 "left out" each time. The final time only one subject was left out. To be considered successful, such rules should correctly classify substantially more than 50% of the test set subjects. The "jackknifing" technique is generally taken as a method to appraise the prospective performance of diagnostic classification rules when the rules are developed on small data sets. In its original form, "jackknifing" referred to the "leaving out" of single subject test sets. The "leaving out" of larger test sets, 4 in our case, is a more conservative procedure.

RESULTS

Electroencephalographic (EEG) Evaluation: EEG frequency spectra derived from 19 children with high dentine lead concentration were compared with those derived from 22 of their classmates with low dentine lead concentration. The high lead children differed significantly from their low lead counterparts for a number of EEG spectral features (Table 1). The distribution of these differences among the various combinations of recording conditions, electrode position and frequency band was decidedly non-random.

By far the largest number of differences occurred in spontaneous EEG recorded in the state of relaxed wakefulness with the eyes closed (EC). Moreover, these differences clustered with respect to frequency band and spatial topography. Two patterns are clearly evident. First, the high lead group had consistently higher percentages of slow frequency delta (0.5-3.5 Hz) activity in the EEG recorded from a series of adjacent electrodes covering the central, parietal and occipital regions of the head bilaterally and extending forward into the right prefrontal area (Figure 2).

The second pattern of differences in the eyes closed EEG was a decrease in the percentage of alpha (8-12 Hz) activity in the occipital lobes and the midline central parietal region of the high lead subjects (Figure 3).

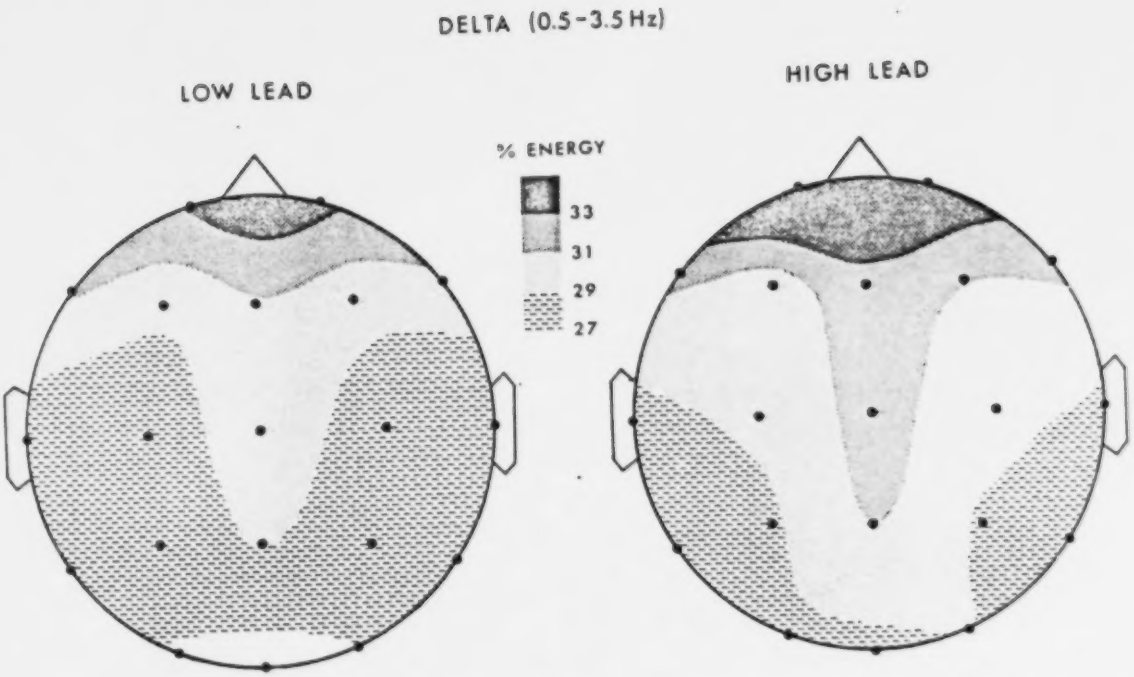


Figure 2: Topography of delta EEG spectral energy in high and low lead children. EEG recorded while subjects were relaxed, alert with eyes closed. Delta energy was calculated as the percentage of total EEG spectral energy in the frequency range 0.5-3.5 Hz. This was done for each electrode derivation from the mean EEG spectrum of the high and low lead group, respectively, and topographical maps of delta energy were constructed by linear interpolation based upon the values of the nearest 3 electrode points (11).

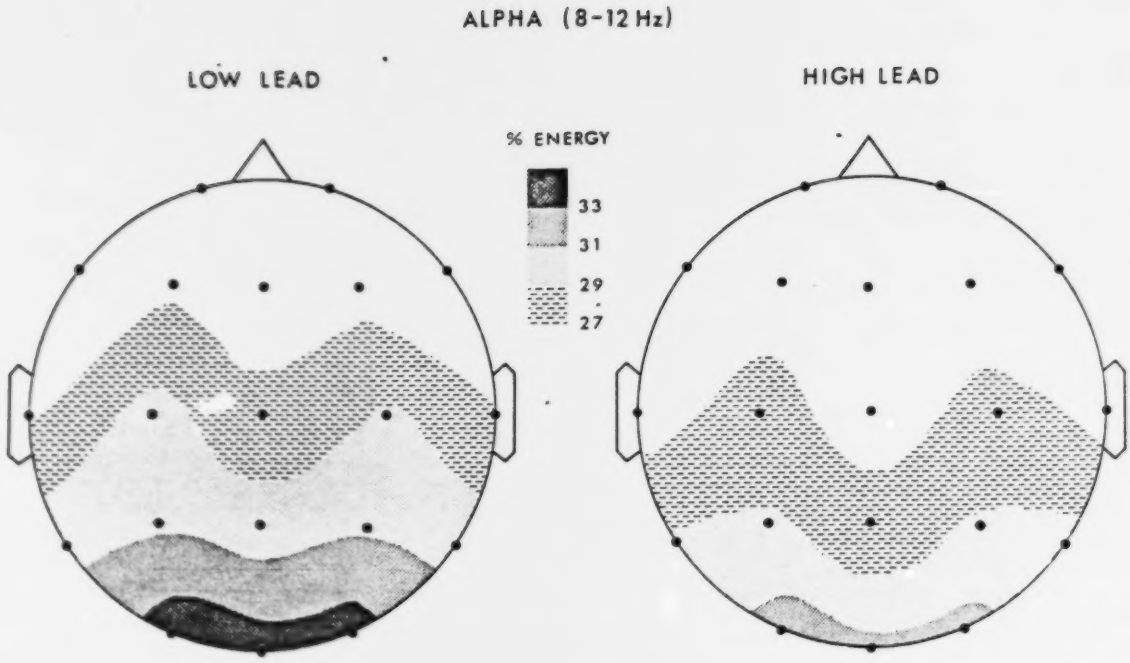


Figure 3: Topography of alpha (8-12 Hz) EEG spectral energy in high and low lead children. Same recording condition as in Figure 2. See legend of Figure 2 for further details.

Somewhat similar regional patterns of EEG differences were seen in the eyes open (EO) condition, but to a much smaller extent (Table 1); the high lead group had significantly larger percentages of delta activity in the midline, central and parietal regions (CZ and PZ). It is interesting to note that these were the same two electrode positions which showed the greatest differences in delta activity in the eyes closed EEGs. During the eyes open state, the high lead group also had decreased percentages of alpha activity; however, in contrast to the eyes closed condition, this occurred in the prefrontal area rather than the occipital area.

No statistically significant differences occurred in any of the comparisons between spectral values derived from EEGs recorded during the conditions of hyperventilation or post-hyperventilation. Likewise, the high and low lead groups did not differ anywhere in the theta (4-7.5 Hz) or beta (12.5-31.5 Hz) frequency ranges.

Discrimination Between High and Low Lead Groups Based Upon EEG and Psychologic Features: Merit Value analysis culled from the available features those with the greatest potential for discriminating between high and low lead groups. EEG and psychologic features were considered both alone and in combination. Table 2 lists the 6 features in each category with the highest Merit Value.

The power of these features to discriminate between the high and low lead exposure was tested with direct and stepwise discriminant analyses. For both types of analysis, the 4 "best" features among, respectively, EEG features alone, psychologic features alone and combined EEG and psychologic features were used as input variables. The most striking result of these discriminant analyses was the marked difference in significance of group separation using combined variables as opposed to EEG or psychologic variables alone (Table 3).

Table 1

COMPARISON OF EEG FEATURES FROM HIGH AND LOW LEAD SUBJECTS BY WILCOXIN-MANN-WHITNEY TWO-SAMPLE RANK TEST

Condition	Electrode	Frequency Band	Mean Percentage of Total Spectral Energy		P-Value
			Low Lead	High Lead	
Eyes Open (EO)	F4	Alpha	25.6	24.5	.05
	FZ	Alpha	25.4	24.3	.05
	CZ	Delta	31.2	32.3	.05
	PZ	Delta	31.0	32.1	.02
Eyes Closed (EC)	F4	Delta	29.9	31.0	.05
	C4	Delta	28.1	29.4	.02
	C3	Delta	28.1	29.3	.05
	P4	Delta	27.7	28.9	.05
	P3	Delta	27.5	28.7	.02
	O2	Delta	27.1	29.1	.02
		Alpha	33.8	31.4	.05
	O1	Delta	26.8	28.5	.02
		Alpha	34.0	31.6	.05
	FZ	Delta	31.2	32.6	.05
	CZ	Delta	30.4	32.0	.01
		Alpha	27.5	26.0	.05
	PZ	Delta	29.5	31.1	.01
		Alpha	30.0	28.2	.05
	OZ	Delta	26.1	27.7	.02
		Alpha	33.9	31.6	.05
Hyperventilation (HV)	NO SIGNIFICANT DIFFERENCES				
Post-hyperventilation (PHV)	NO SIGNIFICANT DIFFERENCES				

Table 2

FEATURES WITH THE GREATEST POTENTIAL POWER FOR DISCRIMINATING BETWEEN HIGH AND LOW LEAD GROUPS AD DETERMINED BY MERIT VALUE ANALYSIS. THE SIX BEST WERE SELECTED FROM, RESPECTIVELY, EEG FEATURES ALONE, PSYCHOLOGIC FEATURES ALONE, AND COMBINED EEG AND PSYCHOLOGIC FEATURES.

Feature	Ambiguity Value	d-Prime	Average Correlation Coefficient	Merit Value
EEG*				
Delta PZ EC	0.64274	0.18900	0.61419	0.37360
Alpha FZ EO	0.76054	0.18780	0.51113	0.36790
Delta OZ EC	0.69427	0.16268	0.55674	0.35811
Alpha OZ EC	0.77362	0.18660	0.61946	0.32671
Alpha PZ EC	0.68875	0.17703	0.68980	0.32517
Alpha CZ EC	0.75213	0.18660	0.66728	0.31793
PSYCHOLOGIC				
Seashore Rhythm Test	0.68725	0.20215	0.23922	0.49261
Sentence-Repetition Test	0.79442	0.20335	0.38112	0.41039
Performance I.Q.	0.67626	0.19737	0.48870	0.40993
Token Test	0.71324	0.15311	0.37508	0.40597
Full-Scale I.Q.	0.69818	0.25000	0.61164	0.39673
Verbal I.Q.	0.74706	0.23086	0.54674	0.38931
EEG AND PSYCHOLOGIC				
Delta PZ EC	0.64274	0.18900	0.25568	0.49319
Alpha PZ EC	0.68875	0.17703	0.21053	0.48493
Seashore Rhythm Test	0.68725	0.20215	0.26510	0.48399
Verbal I.Q.	0.74706	0.23076	0.39184	0.44094
Full-Scale I.Q.	0.69818	0.25000	0.47989	0.44064
Performance I.Q.	0.67626	0.19737	0.42667	0.43060

*Designation of EEG features is by frequency band, electrode location and recording condition; thus, DELTA PZ EC designates percentage of total spectral energy in the delta (0.5 - 3.5 Hz) frequency band for EEG recorded from the PZ electrode during the state of relaxed wakefulness with eyes closed.

The separation of high and low lead groups using combined variables was highly significant (P = 0.005). By contrast, the P-value using psychological features alone was an order of magnitude less (P = 0.041); however, this value still exceeded conventional standards for statistical significance. The P-value for EEG features alone was P = 0.079.

Significant separation of the high and low lead groups was also demonstrated by stepwise discriminant analysis (Table 4). Here again the most significant discrimination resulted from the use of a combination of EEG and psychologic features (Wilks' lambda = 0.557, p = 0.0002). Note that for EEG features alone, the total discriminatory power resided in a single feature; therefore, Wilk's lambda has little meaning. In this case, the significance of the Mahalanobis distance is a more meaningful statistic ($p \leq 0.01$). For comparison, the significance of the Mahalanobis distance for psychologic features alone is $p \leq 0.025$ and that for combined EEG and psychologic features is $p \leq 0.001$.

Discriminant analysis defines a boundary in multivariate space which optimally separates the two populations. Multivariate space, therefore, is divided into two population domains and any subject whose feature vector falls into one of these domains would be classified as a member of that population. Obviously, the more significant the group separation, the fewer the errors that will be made in such classification. Somplete separation would yield 100% accuracy of classification, whereas two identical populations would result in classification at the chance level of 50%. Hence, the success rate of retrospective classification based upon the discriminant function is another test of the significance of group separation for a set of features.

Retrospective classification of high and low lead children was significantly better than chance (Table 5). This was true for all categories of features. Based upon EEG features alone, 70.7% of subjects were correctly classified. For psychologic features alone, accuracy was 68.3%. Combined psychologic and EEG

Table 3

SEPARATION OF HIGH AND LOW LEAD

GROUPS BY DISCRIMINANT ANALYSIS

EEG Features Alone

Feature	Mean High Lead	Mean Low Lead	F-Statistic	P-Value	Discriminant Coefficient
Delta PZ EC	31.14	29.53	8.32	0.006	-0.863
Delta OZ EC	27.71	26.11	5.96	0.018	-0.050
Alpha OZ EC	31.61	33.86	4.43	0.040	0.160
Alpha FZ EC	24.27	25.39	4.54	0.037	0.478
	Group centroids: high = -11.61, low = 9.24				
	Wilks' Lambda: 0.798				
	Significance of Group Separation by Rao's Approximation: F (4,36) = 2.273, P = 0.079				
Psychologic Features Alone					
Performance I.Q.	103.63	111.50	3.98	0.050	0.626
Seashore Rhythm Test	19.68	22.77	4.44	0.039	0.807
Sentence-Repetition Test	10.90	13.81	7.09	0.011	0.807
Token Test	22.90	25.23	3.53	0.065	0.592
	Group centroids: high = 37.00, low = 42.58				
	Wilks' Lambda: 0.764				
	Significance of Group Separation: F (4,36) = 2.785, P = 0.041				
Combined EEG and Psychologic Features					
Delta PZ EC	31.14	29.53	8.32	0.006	-0.721
Verbal I.Q.	97.26	106.55	6.22	0.016	0.637
Seashore Rhythm Test	19.68	22.77	4.44	0.039	0.549
Alpha PZ EC	28.20	30.00	4.78	0.033	0.568
	Group centroids: high = -14.20, low = -10.91				
	Wilks' Lambda: 0.661				
	Significance of Group Separation: F (4,36) = 4.61, P = 0.005				

Table 4

SEPARATION OF HIGH AND LOW LEAD

GROUPS BY STEPWISE DISCRIMINANT ANALYSIS

EEG Features Alone

Step	Feature Entered	F to Enter
1	Delta PZ EC	8.33

Significance of Mahalanobis Distance
$F(1,39) = 8.33$, $p < 0.01$

Psychologic Features Alone

Step	Feature Entered	F to Enter
1	Full-Scale I.Q.	7.13
2	Sentence-Repetition Test	2.85
3	Seashore Rhythm Test	1.47

Wilks' Lambda = 0.756, P = 0.015
Significance of Mahalanobis Distance
$F(3,37) = 3.97$, $p < 0.025$

Combined EEG and Psychologic Features

Step	Feature Entered	F to Enter
1	Delta PZ EC	8.33
2	Full-Scale I.Q.	14.70
3	Verbal I.Q.	1.27
4	Performance I.Q.	1.12

Wilks' Lambda = 0.557, P = 0.0002
Significance of Mahalanobis Distance
$F(4,36) = 7.15$, $P < 0.001$

features yielded the most successful classification with 75.6% correct.

Prospective Classification of Subjects into the High or Low Lead Group Based Upon EEG and Psychologic Features: A better test of the discriminating power of a set of features is prospective classification. In retrospective classification one defines and tests a discriminant function using the same subjects. In prospective classification, on the other hand, classification rules are developed on one set of subjects (the "training" set) and tested on a separate set (the "test" set). Clearly, in order for prospective classification to succeed a greater than a chance level, the subjects must fall into two distinct clusters in multivariate space.

Based upon the 6 best combined EEG and psychologic features we were able to classify test sets of children as high or low lead with an overall accuracy of 65.9% well above chance (Table 6). Moreover, the additive discriminating power of EEG and psychologic features was clearly demonstrated by this procedure; prospective classification using either EEG or psychologic features alone yielded only chance levels of classification (48.8% and 41.5% respectively). This indicates that the separation of high and low lead subjects into two distinct clusters is much more prominent in a multivariate space consisting of both EEG and psychologic features than it is in one consisting of either type of feature alone.

Speech and Auditory Evaluation:

Each subject received the following tests, administered singly by examiners in the blind to the child's lead status:

1. Pure Tone Audiometry: Tones were delivered to each ear separately at 250 Hz, 500 Hz, 1 K Hz, 2K Hz, 3K Hz, 4K Hz, 6K Hz, and 8K Hz.

Table 5

RETROSPECTIVE CLASSIFICATION OF SUBJECTS

BASED UPON STEPWISE DISCRIMINANT ANALYSIS

Features	*Percentage of Subjects Correctly Classified*		
	Low Lead	*High Lead*	*All*
EEG Alone	68.2	73.7	70.7
Psychologic Alone	72.7	63.2	68.3
Combined EEG and Psychologic	77.3	73.7	75.6

Table 6

PROSPECTIVE CLASSIFICATION OF SUBJECTS

USING "JACKKNIFING" PROCEDURE

Features	*Percentage of Subjects Correctly Classified*		
	Low Lead	*High Lead*	*All*
EEG Alone	36.4	63.2	48.8
Psychologic Alone	50.0	31.5	41.5
Combined EEG and Psychologic	59.1	73.7	65.9

2. Tone Decay Test: In order to determine if auditory adaptation is present, a Modified Tone Decay Test was administered at 1000 Hz and 4000 Hz.
3. Speech Discrimination: (a) Speech intelligibility was estimated by using phonetic balanced word lists. Stimuli were presented at 40 dB SL re: the hearing level for speech using the open response format. (b) Speech in words function was estimated using phonetic balanced word lists at a signal to noise ratio of +10.
4. Speech Reception Threshold: Two syllable words (Spondees) are uttered to the subject in 2 dB decreasing steps until the subject can no longer repeat words correctly. The SRT is defined at 2 dB above the failure level.
5. Staggered Spondaic Word Test was administered. This test is reported to be sensitive to central auditory dysfunction. Overlapping spondaic words were fed into each ear separately, and the individual then asked to report on what was heard. This may be diagrammed as follows:

	Left Ear	Both Ears	Right Ear
Input:	up	stairs down	town

Correct Report: "upstairs" and "downtown"

Incorrect Report: "updown" and "up town"

Errors are reported for both ears in the competing and noncompeting circumstance.

6. Goldman-Fristoe-Woodcock Auditory Selective Attention Test: The subject is asked to identify pictures corresponding to words uttered

on a tape under three conditions: (a) against a background of fan-like noise, (b) against a background of cafeteria noise, (c)against a background of a verbal story. The signal-to-noise ratio varies from a positive to negative ratio in each situation. Percentile scores for each age are calculated.

These tests were administered in fixed order to conform with the assessment protocol of the speech clinic. While order effects are a possible risk, these would be experienced by both high and low lead subjects.

Data Analysis:

The speech and hearing outcomes were compared using ANACOVA. Distributions of outcomes were first evaluated and appropriate transformations (either log or z-score) were applied to non-Gaussian distributions of data. Several outcomes were severely non-normal in distribution (e.g. bimodal). These were dichotomized as close to the median as possible. Tone Decay and Pure Tone Audiometry Variables did not require transforming. The following variables were transformed:

Variable	*None*	*z Score*	*log*	*Dichotomize*
SRT Right				✓
SRT Left				✓
SSW Right Non-competing		✓		
SSW Left Non-competing		✓		
SSW Right Competing		✓	✓	
SSW Left Competing		✓	✓	
GFW - fan				✓
cafeteria		✓		
voice	✓			

(transformed variables, continued)

Variables	*None*	*z Score*	*log*	*Dichotomize*
Speech Discrimination:				
quiet - right				✓
quiet - left		✓		
noisy - right		✓		
noisy - left		✓		

Five covariates identified as important predictors of outcome in the earlier neuropsychological study (4) were employed in the ANACOVA to control for socioeconomic confounding. These covariates were: mother's education, father's social class, family size (number of pregnancies), mother's I.Q. (Peabody Picture Vocabulary Test), and mother's age at subject's birth. Pure tone audiogram results are shown in Table 7.

The F-ratios and p values on all tests with both raw and transformed data are displayed in Tables 8 and 9. While no significant differences at the $p = 0.05$ level were found on the pure tone audiometric examinations, low lead subjects had lower mean values (indicating greater accuracy) on 13 of 16 outcomes. The 4 tests of speech processing were comprised of 17 outcome measures. Four outcomes differed at $p \leq 0.05$ (SSW left non-competing, GFW voice and total score, and speech descriminations, quiet, left). Of the 17 outcomes, 15 tended to favor one low lead group.

The speech data suggest low lead affects speech processing, but replication, with a smaller battery of tests is indicated.

Table 7

MEAN AUDIOMETRIC VALUES (± STANDARD DEVIATION)

OF HIGH AND LOW LEAD SUBJECTS

Pure Tones		*High Lead*	*Low Lead*
Right	250	12.50 ± 10.1	11.09 ± 7.2
	500	11.07 ± 8.1	9.78 ± 5.3
	1000	8.21 ± 9.9	6.52 ± 4.9
	2000	5.00 ± 6.5	2.83 ± 3.9
	3000	8.61 ± 8.9	8.47 ± 7.0
	4000	7.50 ± 8.7	6.95 ± 9.6
	6000	15.00 ± 11.1	14.13 ± 12.5
	8000	11.43 ± 13.2	12.17 ± 10.1
Left	250	11.07 ± 6.8	8.48 ± 4.6
	500	9.00 ± 4.4	7.17 ± 4.5
	1000	5.71 ± 5.5	4.34 ± 7.0
	2000	2.14 ± 3.2	2.17 ± 5.6
	3000	7.14 ± 4.7	6.74 ± 5.8
	4000	5.36 ± 4.6	5.87 ± 5.6
	6000	13.57 ± 7.4	11.74 ± 7.5
	8000	15.35 ± 16.1	10.22 ± 7.0

Table 8

MEAN VALUES AND SIGNIFICANCE TESTS

(AFTER ANALYSIS OF COVARIANCE) FOR TESTS OF SPEECH PROCESSING

	$\overline{X}$ *High Lead*	$\overline{X}$ *Low Lead*	**Significance*
Right SRT	5.28	6.08	
Left SRT	4.86	5.13	
SSW - right non-competing	24.57	25.31	
SSW - right competing	38.14	39.60	
SSW - left competing	41.14	41.09	
SSW - left non-competing	22.14	24.65	p = .048
SSW - right	31.65	32.70	
SSW - left	33.21	33.69	
SSW - total	31.57	33.31	
GFW - fan	50.77	66.78	
GFW - cafeteria	36.62	47.48	
GFW - voice	53.23	77.35	p = .05
GFW - total	35.92	61.39	p = .035
Speech Disc.: Quiet right	93.71	96.17	
left	91.86	96.25	p = .036
Noisy right	72.57	74.44	
left	74.00	72.00	

**after appropriate transformation and adjustment for covariates*

Table 9

OUTCOME OF SPEECH PROCESSING: VALUES GIVEN ARE F RATIOS AND P VALUES AFTER ANALYSIS OF COVARIANCE OF RAW AND TRANSFORMED DATA WITH ALL COVARIATES, AND SELECTED COVARIATES FOR EACH ITEM

	All Covariates Raw		*Selected Covariates Raw*		*All Covariates Raw*		*Selected Covariates Transformed*	
	F	*P*	*F*	*P*	*F*	*P*	*F*	*P*
SRT Right	1.09	NS	-	-	1.2	NS	1.5	NS
SRT Left	.7	NS	-	-	.05	NS	.49	NS
SSW - right non-competing	.02	NS	.09	NS	.02	NS	.01	NS
right competing	.07	NS	.07	NS	.01	NS	.01	NS
left competing	.08	NS	.2	NS	.085	NS	.00	NS
left non-competing	4.2	.048	3.7	.06	4.2	.048	2.5	NS
right	.05	NS	.14	NS	.05	NS	.16	NS
left	.00	NS	.08	NS	.00	NS	.09	NS
total	.3	NS	.5	NS	.31	NS	.6	NS
GFW - fan	1.65	NS	.97	NS	1.5	NS	.45	NS
cafeteria	1.5	NS	1.2	NS	1.57	NS	2.3	NS
voice	4.2	.05	8.2	.007	-	-	-	-
total	4.9	.035	8.4	.006	-	-	-	-
Speech Discrimination								
Quiet right	1.9	NS	.97	NS	.2	NS	1.1	NS
left	6.2	.019	9.2	.004	3.5	.069	4.7	.036
Noisy right	.7	NS	.04	NS	1.05	NS	1.2	NS
left	.14	NS	.14	NS	.089	NS	0	NS

Study II: Teachers' Behavioral Ratings in Lowell School Children in Relation to Dentine Lead Levels

Study Sample: Children attending first grade in Lowell, Massachusetts in academic years 1977 and 1978 comprised the cohort sampled. After two months' experience with each class, teachers were released from class to evaluate the subjects on an 11-item teachers' rating questionnaire (see appendix 1 for questionnaire format).

In evaluating each item, a good outcome (i.e. Hyperactive? "No" or Able to follow directions? "Yes") was scored as 1, a bad outcome scored as 0. Thus, a score of 11 would be perfect, a score of 0 very poor, and a score of 5 midrange. This sum score was only used to select patients for follow-up. Item analyses were also done for each group of subjects.

Shed decisuous teeth were collected by the teachers who were asked to note whether an appropriate vacant socket was found in the donor's mouth. Teeth were collected from 1,273 children (624 males, 652 females) who were evaluated by the questionnaire.

Children of both sexes were evaluated with respect to teachers' questionnaire and dentine lead level. Only male children were candidates for follow-up with family interviews and psychological testing. Within each class, all male children who were designated as "Hyperactive - yes" on the teachers' rating scale were selected for follow-up. In the same class, we attempted to select another male identified as "Hyperactive - no" with a sum score of 10 or 11 (referred to as "control"). We also attempted to select from the same class a child identified as "Hyperactive - no" with a sum score of 5-7 (referred to as "midrange"). Follow-up was attempted on a total of 447 children.

Essentially complete follow-up was obtained on a total of 215 children. Incomplete but substantial follow-up data was collected on an additional 18 children. The distribution of the 447 children selected for follow-up and the 215 children with complete follow-up data are displayed in Table I.

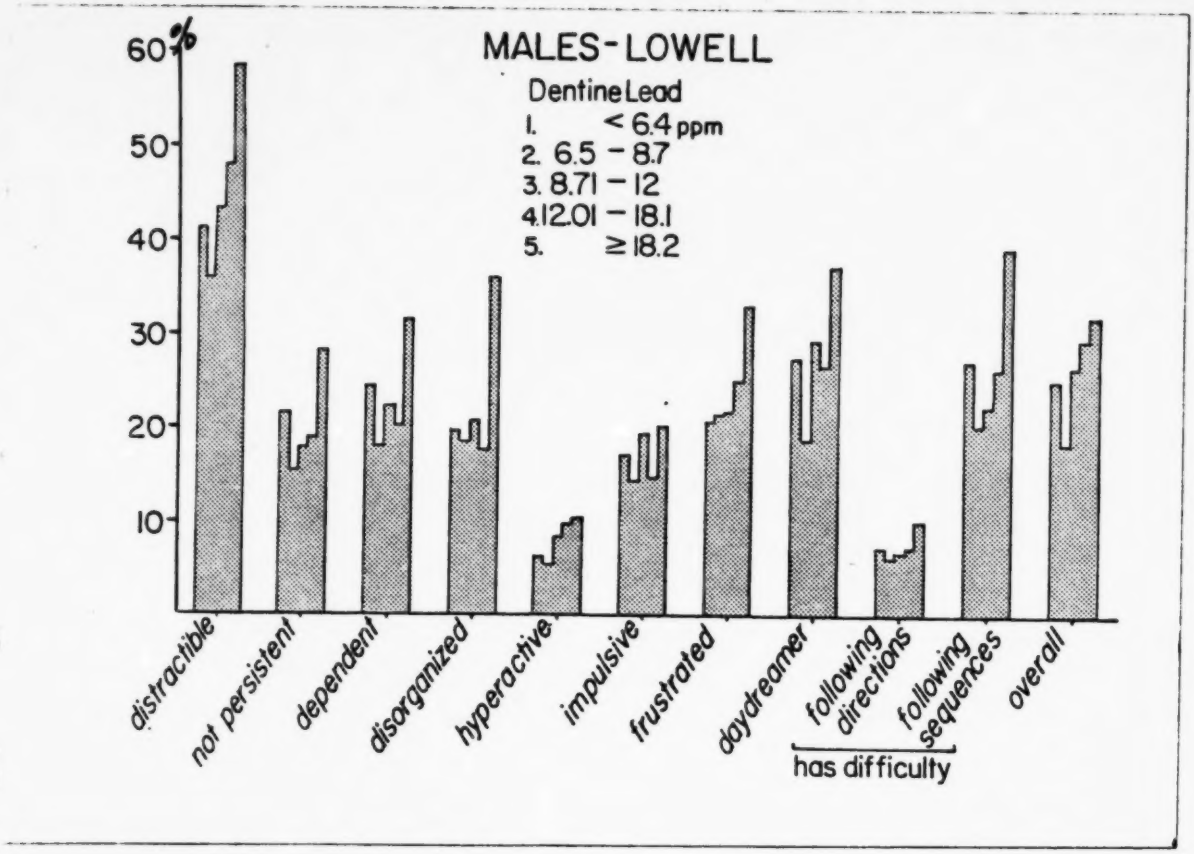
	Selected for Follow-up	*Pb Avail.*	*Follow-up Completed*	*Pb Avail.*
"hyperactive" males	151	53	Yes	36
" control" males	160	78	Yes	53
"midrange" males	136	60	Yes	41

In addition, a number of performance tests were utilized to evaluate those children who were followed up.

Data Analysis: The classroom behavior of students from Lowell, Massachusetts in relation to their dentine lead levels was evaluated in two ways. In the first evaluation, subjects were classified into five groups according to their dentine lead level. Group 1 $\leq$ 6.4 ppm; Group 2 = 6.5 to 8.7 ppm; Group 3 = 8.71 to 12 ppm; Group 4 = 12.01 to 18.1 ppm; Group 5 $\geq$ 18.2 ppm. These boundaries were selected to be similar to those used in the study by Needleman et al. (1979), but were modified slightly by examination of discontinuities in the dentine lead distributions. Males and females were then separated, and the proportion of negative reports on each item of the teachers' rating scale calculated for each group. Figures 4 and 5 display the increased incidence of negative reports in relation to increased dentine lead level.

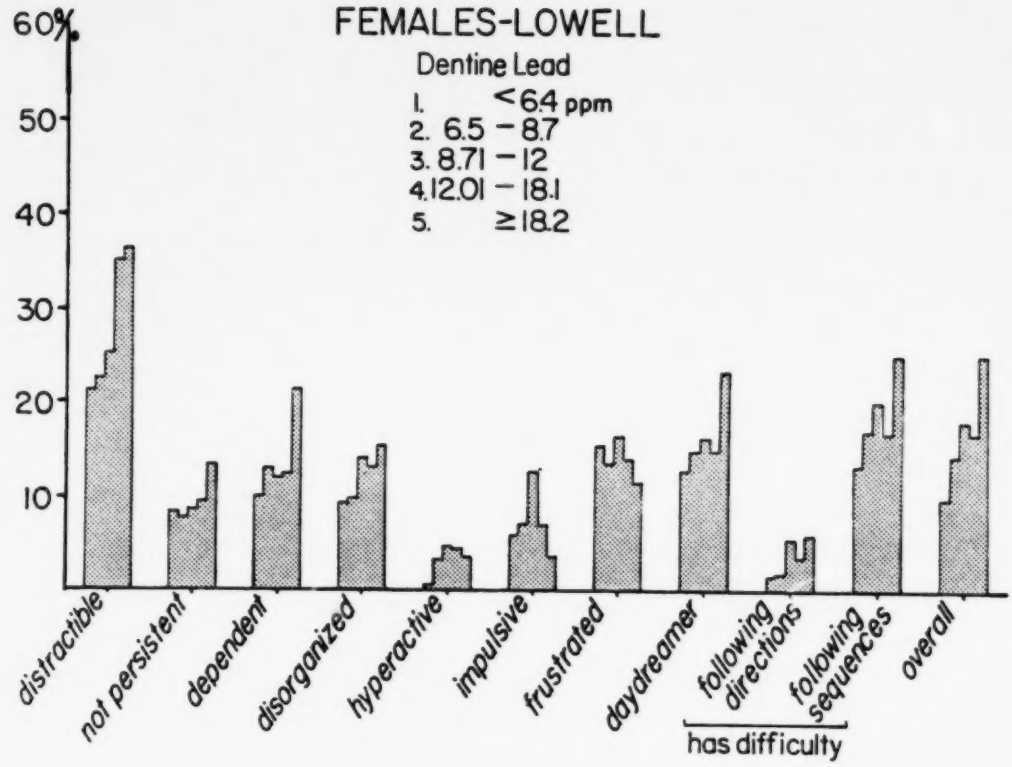
In the second evaluation, male subjects were followed up and socioeconomic data obtained from parental questionnaires. These data were treated as covariates and the relationship of lead to teachers' ratings evaluated by multiple logistic regression analysis. This allowed us to more clearly estimate the role of lead in classroom behavior.

Figure 4



The relationship between negative teachers' ratings and dentine lead level in males. Each sample was classified into 5 groups according to dentine lead level. Each item was then scored. Within each item, Group 1, lowest lead level, is at the left; Group 5, highest lead level, is at the right.

Figure 5



The relationship between negative teachers' ratings and dentine lead levels in females. Each sample was classified into 5 groups according to dentine lead level. Each item was then scored. Within each item, Group 1, lowest lead level, is at the left; Group 5, highest lead level, is at the right.

Evaluation of Teacher Ratings: A cluster analysis of the 11 items in the teachers rating scale was performed in order to reduce the outcome space and thereby alleviate the potential problems of multiple comparisons. Two separate cluster analyses were performed for each sex, utilizing tetrachoric and Pearson correlation coefficients. In addition, factor analyses of the teachers rating scale were performed as a validation procedure. The various procedures all yielded similar results for each sex. The resulting clusters for males are defined below. (Because follow-up data was only obtained for males, final data analysis was restricted to males.) Two items (frustrated and day dreams) were not segregated, and were treated as separate outcomes.

Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
not persistent	hyperactive	distractible	frustrated	daydreams
dependent	impulsive	disorganized		
poor overall functioning				
less able to follow simple directions				
less able to follow sequences of directions				

Cluster scores were assigned on a monothetic basis. The distributions of scores within the clusters (males) were evaluated in order to determine the most sensitive method for scoring the clusters dichotomously. The distributions are displayed below: (Entries are the number scoring yes on the variable given their total score.)

Cluster 1

Total # Yes	Persist	Independent	Follow Simple Directions	Follow Seq.	Overall	Total
0						126
1	16	4	132	2	2	156
2	59	16	122	41	26	134
3	91	79	125	48	50	134
4	147	154	175	113	175	188
5						1802

Cluster 2

Total # Yes	Hyperactive	Disorganized	Total
0			1458
1	16	191	207
2			131
			1896

Cluster 3

Total # Yes	Distractible	Disorganized	Total
0			953
1	422	40	462
2			378
			1793

It is clear from the results for Cluster 1 that a great majority of the cases wich received one yes score for the entire cluster obtained it from the item "follow simple directions". It was, therefore, decided to eliminate this item from the cluster. Thus, Cluster 1 was evaluated as a 4-item cluster in the following manner. All cases who had not received a "yes" response to any of the four items were given a cluster score of 0. After eliminating ineligible cases (lead poisoning, etc.), a total of 243 cases received a score of 0. All cases who had received a "yes" to every one of the four items were given a cluster score of 1. A total of 1063 cases received a score of 1. All other cases (i.e., all cases which had not received the same score on every item) were eliminated from the subsequent analyses.

The results for Cluster 2 indicated that most cases which received a single "yes" within the cluster, received it for the impulsivity item. Since it was felt that this was reflective of the hesitancy of teachers to label children as hyperactive, it was decided to pool cases which had received at least one "yes" score in the cluster. Thus, there were 1,446 cases who had been scored "no" for both items and received a 0 for the cluster. A total of 332 cases had received a "yes" for at least one item and, therefore, were scored as 1 for the cluster.

Cluster 3 exhibited a similar pattern to Cluster 2 in that a large proportion of the cases with discrepant results for the two items followed a particular pattern--in this case, a "yes" score for distractibility. However, since no underlying reason could be identified for this pattern, the strategy utilized for Cluster 1 was applied to Cluster 3. Thus, all cases with discrepant results for the two items were eliminated. Cases with a "no" response to both items (375 cases) were given a cluster score of 0. Cases with a "yes" response to both items (941 cases) were given a cluster score of 1.

Multiple Logistic Model: The effect of dentine lead level upon each of the 3 clusters was evaluated utilizing a multivariate logistic model:

$$\log \left(P_j/1-p\right) = \sum_{i=1}^{n} Bi \times i,$$

P_j = probability of a score of 1 on a cluster for subjects

x_i, = predictor variable i, for subjects

B_i = effect of predictor variable i

The model was formulated so that the maximum number of available subjects was utilized and had the following features:

1. a main effect indicator (0-1) variable was included which had the value 1 if follow-up information was available; 0 otherwise.
2. a main effect indicator variable was included which had the value 1 if dentine lead data was available; 0 otherwise.
3. the follow-up variables were transformed into sets of discrete indicator variables (Table 10 lists all follow-up variables utilized in the analysis and their categorizations. All follow-up variables were scored as 0 if follow-up data had not been obtained.

Thus, the model took on the following form:

$$\log \left(P/1-p\right) = I_1 + I_1 \left(\sum_{i=1}^{n} B_i X_i\right) + I_2 + I_2 \left(\sum_{j=1}^{n} = X_j L_j\right.$$

I_1 = 1 if follow-up data available

0 if otherwise

x = set of indicator variables for follow-up data

I_2 = 1 if dentine lead data available

0 otherwise

L = set of indicators for lead data

Representation of continuous predictor variables by sets of indicator variables was deemed desirable. This approach was utilized since it was likely that the relationship between the covariates and the logit of the probabilities was not linear in form. Therefore, utilization of a continuous variable would be inappropriate without employing complex functions such as polynomials. The generation of discrete classes was based upon both theoretical and true distribution of each variable. A number of cases had two to four dentine lead determinations. Multiple determinations were examined for concordance. If all determinations were determined to be concordant, an average lead value was determined and used in the analysis. If two of three (1 case) or three of four (3 cases) readings were concordant and markedly different from the remaining result, the discordant result was excluded before averaging. If two or more results were discordant, the case was treated as if no dentine lead data was available (10 cases).

Method of Determining the Effect of Lead Upon Behavioral Clusters: The goal of the analysis was to evaluate the effect of dentine lead level on the behavioral cluster scores after controlling for socioeconomic - environmental effects. In order to achieve this goal, the following sequence of analyses was performed for each cluster:

1. Determination of the follow-up variables which had a significant ($p < .05$) readership with the cluster by using stepwise multiple logistic regression. This model automatically included the main effect indicator variables for the presence of a dentine lead assay result. The dentine lead level indicator variables were not included at this stage of the analysis.

Table 10

COVARIATES AND CATEGORIES SCORED IN LOGISTIC

REGRESSION ANALYSIS OF TEACHER'S RATINGS

Variable	*Referrent Category*	*Scored Categories*
Race	White	Nonwhite
Age	1968	1969
		1970
		1971
		1972-1973
Birthweight	111-120 ounces	⟨ 88
		89-110
		121-134
		⟩ 135
Delivery	Vaginal	Caesarian
Pregnancy Length	40 months	⟨ 37
		38-39
		⟩ 41
Infant's time in hospital	5 days	5-7
		⟩ 7
Mother and child left hospital together	Yes	No
Mother's education	12 years	⟨ 8
		9-11
		13-15
		⟩ 16
Father's education	12 years	⟨ 8
		9-11
		13-15
		⟩ 16
Mother Hollingshead: occupation	1-5	6-7
Father Hollingshead: occupation	5	1-4

Table 10 (continued)

Variable	*Referrent Category*	*Scored Categories*
Mother head of household	No	Yes
Number of hospitalizations	0	1-2
		> 3
Number of head injuries	0	> 1
Number of seizures	0	> 1
Number of illnesses	0	> 1
Immunizations	Yes	No
Other health problems	No	Yes
Medications	No	Yes
Enuresis	No	Yes
Number of pregnancies	1	2-3
		4-5
		> 6
Miscarriages	0	> 1
Birth order of child	first	second
		third
		fourth
		> fourth
Mother's IQ	101-115	< 85
		86-100
		116-125
		> 126
Mother's marital status	married	unmarried
Mother's age at birth of child	20-25 years	< 19
		26-30
		> 31
Attended preschool	Yes	No
Attended daycare	Yes	No
Dentine lead	0-6.37 ug	6.37-8.70 ug
		8.71-12.0 ug
		12.01-18.2 ug
		> 18.2 ug

2. Determination of the significance and dose-response pattern of the lead effect. This was done by adding the set of dentine lead indicator variables to the multivariate model which was derived in step 1.

RESULTS

Cluster 1: Effect of Follow-up Variables: Table 11 displays the results for the variables which were selected by the stepwise logistic regression. The relative risks for the birthweight variable indicate an increase for both the lowest and higher birthweight groups. Although the risk for those not attending daycare appears quite large, only 12 children in the sample did attend daycare; thus, the estimate is probably unstable.

Cluster 1: Lead Effect: The addition of the set of lead level variables to the model derived in step 1 did not yield evidence of a significant lead effect for this cluster. The results are displayed in Table 12. The risk in the highest lead level group is essentially equal to the risk in the lowest lead level group (referrent).

Cluster 2: Effect of Follow-up Variables: The results of the stepwise logistic regression utilizing the follow-up variables alone are shown in Table 13. The most notable effect is that of mother's education. Children whose mothers had less than 9 years of education had approximately 17 times the risk of being perceived to exhibit hyperactive/impulsive behavior than children whose mothers graduated from high school (12 years) but went no further. An inverse relationship between years of school and a problematic score on this cluster can be seen very clearly upon examining the relative risks:

Years of Education	Relative Risk
8	17.07
9-11	1.93
12	1.00
13-15	.42
16	.16

Table 11

CLUSTER 1: N - 1306

Variable	*N*	*Value*	*Regression Coefficient*	*Coefficient Std. Error*	*Relative Risk*	*Entry Order*	*P to Enter*
Intercept			1.364	15.62			
I_1	136	Follow-up Done	-0.206	-0.44	.81		
I_2	465	Lead Done	0.331	2.12	T.39		
Daycare	12	Yes	5.092	1.25	162.67	1	.036
Birth-weight	12	$\leq$ 88 oz.	0.749	0.65	2.11	2	.041
	34	89-110	-0.888	-1.45	.41		
	36	121-134	0.842	1.10	2.32		
	21	$\geq$ 135	1.447	1.28	4.25		

Table 12

ADDITION OF DENTINE LEAD LEVEL VARIABLES

TO THE MODEL DESCRIBED IN TABLE 11 (CLUSTER I)

Dentine Lead Level (ppm)	*N*	*Regression Coefficient*	*Coefficient/ Standard Error*	*Relative Risk*
0.00 - 6.36	146	Referrent		1.0
6.37 - 8.70	103	.404	1.10	1.50
8.71 -12.0	90	.565	1.41	1.76
12.01 -18.2	83	.196	0.53	1.22
$\geq$ 18.2	43	-.117	-0.27	0.89

TABLE 13

CLUSTER 2

Variable	*N*	*Value*	*Regression Coefficient*	*Coefficient Std. Error*	*Relative Risk*	*Entry Order*	*P to Enter*
Intercept			-1.561	-19.85			
I_1	195	Follow-up Done	1.004	1.89	2.73		
I_2	618	Lead Done	-0.244	- 1.79	.78		
Birthweight (referrent = 111-120 oz.)	N=50					1	.014
	17	$\leq$ 88 ozs.	-1.499	- 2.15	.22		
	57	89-110	-1.104	- 2.30	.33		
	48	121-134	-1.154	- 2.42	.32		
	23	$\geq$ 135	-0.439	- .70	.64		
Mother's education (referrent = 12 yrs.)	N=87					2	.018
	19	$\leq$ 8 years	2.838	2.86	17.07		
	44	9-11 years	0.659	1.43	1.93		
	28	13-15 years	-0.859	- 1.31	0.42		
	17	$\geq$ 16 years	-1.845	- 1.53	0.16		
Mother's IQ (referrent = 101-115 pts.)	N=44					3	.018
	19	$\leq$ 85	-0.678	- .83	0.51		
	50	86-100	0.980	2.05	2.66		
	38	116-125	0.490	0.89	1.63		
	29	$\geq$ 126	0.900	1.48	2.46		

TABLE 13

CLUSTER 2

(continued)

Variable	*N*	*Value*	*Regression Coefficient*	*Coefficient Std. Error*	*Relative Risk*	*Entry Order*	*P to Enter*
Father's education (referrent = 12 yrs.)	N=98					4	.036
	12	≤ 8 years	0.972	1.61	2.64		
	50	9-11 years	0.064	0.19	1.07		
	21	13-15 years	1.533	2.76	4.66		
	14	≥ 16 years	1.001	1.01	2.72		
Pregnancy length (referrent = 40 weeks)	N=124					5	.009
	16	≤ 37 weeks	0.090	0.13	1.09		
	24	38-39 weeks	0.274	0.52	1.31		
	31	≥ 41 weeks	-1.233	-2.17	0.29		

Table 14

ADDITION OF DENTINE LEAD LEVEL VARIABLES

TO THE MODEL DESCRIBED IN TABLE 13 (CLUSTER II)

Dentine Lead Level (ppm)	*N*	*Regression Coefficient*	*Coefficient/ Standard Error*	*Relative Risk*
0.00 - 6.36	179	Referrent		1.0
6.37 - 8.70	125	-.433	-1.27	0.65
8.71 - 12.0	123	0.113	0.36	1.12
12.01 - 18.2	123	0.177	-0.54	0.84
$\geq$ 18.2	65	0.286	0.78	1.33

Overall P to enter = 0.414

It should be noted that these are estimates controlling for the other variables in the model. It should also be noted that a significantly elevated risk is found in children of mothers whose IQ is between 86 and 100 as compared to those whose mothers had IQs of 101-115. Also, children who were born after very long pregnancies had a low risk on this cluster.

It is more difficult to explain the patterns in birthweight and father's education, but the interaction of the 8 variables in the model should be kept in mind.

Cluster 2: Lead Effect: The set of lead level indicator variables was added to the model derived in step 1. The results are displayed in Table 14. Although the highest risk is in the group with the highest lead level, the effect is not significant nor is the overall effect for the set of lead variables. There is little evidence of a dose-response effect in these results for this cluster.

Cluster 3: Effect of Follow-up Variables: The model resulting from the stepwise regression on the follow-up variables is shown in Table 15. The results for mother's education show a clear inverse relationship between years of education and the child's risk on this cluster as shown below:

Years of Education	Relative Risk
8	3.62
9-11	3.78
12	1.00
13-15	.54
16	.19

Table 15

CLUSTER 3 - N = 1316

Variable	*N*	*Value*	*Regression Coefficient*	*Coefficient Std. Error*	*Relative Risk*	*Entry Order*	*P to Enter*
Intercept			-0.898	-11.75			
I_1	135	Follow-up Done	1.362	3.06	3.90		
I_2	452	Lead Done	-.303	- 1.36	0.74		
Birthweight (referrent = 111-120 oz., N=33)						1	.007
	12	$\leq$ 88 oz.	-1.983	- 2.05	0.14		
	39	89-110	-0.597	- 1.03	0.55		
	33	121-134	-1.950	- 3.10	0.14		
	18	$\geq$ 135	-1.944	- 2.51	0.14		
Mother's education (referrent = 12 yrs., N = 67)						2	.006
	11	$\leq$ 8 years	1.287	1.24	3.62		
	32	9-11 years	1.329	2.47	3.78		
	15	13-15 years	-0.622	-0.83	0.54		
	10	$\geq$ 16 years	-1.680	-1.57	0.19		

Table 16

ADDITION OF DENTINE LEAD LEVEL VARIABLES

TO THE MODEL DESCRIBED IN TABLE 15 (CLUSTER 3)

Dentine Lead Level (ppm)	*N*	*Regression Coefficient*	*Coefficient/ Standard Error*	*Relative Risk*
0.00 - 6.36	131	Referrent		1.00
6.37 - 8.70	94	-0.242	-0.72	0.79
8.71 -12.00	92	0.028	0.01	1.00
12.01 -18.20	83	-0.456	-0.14	0.96
≥18.20	52	1.030	2.93	2.80

overall p to enter = .013

Table 17

Frustratable

Variable	*N*	*Value*	*Regression Coefficient*	*Coefficient Std. Error*	*Relative Risk*	*Entry Order*	*P to Enter*
Intercept			-1.215	-17.04			
I_1	215	Follow-up Done	0.346	1.42	1.41		
I_2	616	Lead Done	-0.017	- 0.14	0.98		
Mother's education (referrent = 12 yrs., N = 107)						1	.030
	13	$\leq$ 8 years	-5.232	- 1.31	0.01		
	55	9-11 years	0.607	1.69	1.83		
	26	13-15 years	-0.958	- 1.46	0.38		
	14	$\geq$ 16 years	-0.248	- 0.36	0.78		
Preschool (referrent attended)						2	.034
Not attended			.696	- 1.79	0.50		

Table 18

ADDITION OF DENTINE LEAD LEVEL VARIABLES

TO THE MODEL DESCRIBED IN TABLE 17 (FRUSTRATABILITY)

Dentine Lead Level (ppm)	*N*	*Regression Coefficient*	*Coefficient/ Standard Error*	*Relative Risk*
0.00 - 6.36	178	Referrent		1.00
6.37 - 8.70	125	.063	0.22	1.06
8.71 - 12.00	121	.046	0.16	1.05
12.01 - 18.20	123	.211	0.74	1.23
$\geq$ 18.20	69	.631	1.98	1.88

overall p to enter = .3524

Table 19

DAYDREAMING - N = 1778

Variable	*N*	*Value*	*Regression Coefficient*	*Coefficient Std. Error*	*Relative Risk*	*Entry Order*	*p to Enter*
Intercept			-0.959	-14.30			
I_1	195	Follow-up Done	-0.238	- 0.56	0.79		
I_2	619	Lead Done	-0.088	- 0.76	0.92		
Daycare (referrents = attended, N = 181)						1	.017
Not attended	14		-1.899	- 1.90	0.15		
Age of mother (referrent = 20-25 yrs., N = 107)						2	.016
	44	$\leq$19 years	-0.344	- 0.62	0.71		
	30	26-30 years	-1.743	- 3.31	0.18		
	14	$\geq$ 31 years	-0.017	- 0.22	0.90		
Other health (referrent = no, N = 183)						3	.024
Problems	12	Yes	1.517	2.23	4.56		
Father's education (referrent = 12 yrs.)						4	.017
	18	$\leq$ 8 years	0.212	0.32	1.24		
	439	9-11 years	1.159	2.40	3.19		
	31	13-15 years	-0.053	- 0.11	0.95		
	17	$\geq$ 16 years	-1.345	- 1.63	0.26		
Father's occupation Hollingshead (referrent = 5)						5	.042
	77	1-4	0.949	1.96	2.58		
	52	6-7	0.830	1.83	2.29		

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Table 20

ADDITION OF DENTINE LEAD LEVEL VARIABLES

TO THE MODEL DESCRIBED IN TABLE 19 (DAYDREAM)

Dentine Lead Level (ppm)	*N*	*Regression Coefficient*	*Coefficient/ Standard Error*	*Relative Risk*
0.00 - 6.36	177	Referrent		1.0
6.37 - 8.70	126	-0.446	-1.55	0.64
8.71 - 12.00	123	0.047	0.17	1.05
12.01 - 18.20	123	-0.025	-0.09	0.98
$\geq$ 18.20	70	0.577	1.89	1.78

overall p to enter = .059

The results of birthweight indicate those children in the referrent group (111-120 ozs.) were most at risk on this cluster.

Cluster 3: Lead Effect: Addition of the set of lead level indicator variables into the model resulted in a highly significant lead effect (Table 16) (p - .013). The group of children with the highest dentine lead level (> 18.2 ppm) had a significantly higher risk of exhibiting distractible/disorganized behavior than the children with lower lead levels. The ratio of the coefficient to its standard error is asymptotically normally distributed and the coefficient for the highest lead level group is 2.93 standard deviations above 0.0 ($p < .01$).

Cluster 4: Easily Frustrated

Effect of Covariates: Children who attended preschool or whose mothers were less educated were more likely to be scored as easily frustrated.

Effect of Lead: Those children with dentine lead levels greater than 18.2 were at highest risk for this item, and the coefficient for this group is significantly different from zero. The lead effect estimates display a clear dose-response relationship, although the overall p to enter was not significant.

Cluster 5: Daydreaming

Effect of Covariates: Infants who did not attend daycare, and whose mothers were between 26 and 30 years when they gave birth were less likely to be seen to daydream. Infants of better educated fathers were also at lower risk, whereas children with non-specific health problems were at higher risk.

Effect of Lead: Dentine lead levels over 18.2 were associated with increased relative risk for daydreaming, and the lead effect for this group was nearly significant ($P = 0.059$).

DISCUSSION

These studies show that children with elevated lead in their bodies, but who are considered not lead poisoned, differ in their electroencephalograms, in certain areas of speech perception, and in their classroom behavior, from control subjects with lesser amounts of lead.

In setting standards for permissible exposure to lead, intense consideration has been given to determining what alteration constitutes a health effect. The data presented in this report bear on that question, and demonstrate that employing sensitive outcome measures and sophisticated biostatistical techniques enhances the possibility of discovering biologically significant alterations at lower exposure levels.

Smith (10) reported changes in EEG patterns, but only in children who had had encephalopathy. Children entered into this study clearly had no episode of intoxication severe enough to be diagnosed as encephalopathy. (Any child whose mother was told he or she had a lead problem was excluded from consideration.) High lead children tended to have midline slowing (increased delta) and decreased midline alpha activity on EEG. The results obtained here demonstrate the increased sensitivity of quantitative EEG analysis compared to clinical readings.

While only 4 of 17 possible outcomes in the speech processing battery were significantly different at the $p < .05$ level, most outcomes (14/17) evaluated tended to favor the low lead group. The data reported here are in agreement with the findings previously reported by our group (4). In that study, among the areas most sensitive to lead effects were sentence repetition, the token test, and attention.

In our previous study (4), we demonstrated that negative teachers' ratings on most items tended to increase in frequency in direct relationship

to dentine lead levels. The relationship between classroom behavior and dentine lead level is generally similar in this study. The overall incidences of negative reports of each item also resemble those reported earlier in two different cities.

While the finding of a dose response relationship in our previous examination of teachers' ratings was intriguing, we were unable to control for nonlead covariates in that sample. In this study, the follow-up group of males provided an opportunity to evaluate the contribution of lead separated out from other possibly confounding variables. After cluster analysis had reduced the variables to three, the cluster characterized as "distractible-disorganized" was found to be most sensitive to lead, controlling for significant covariates (birthweight and mother's education). A dose-effect relationship between dentine lead level and relative-risk of exhibiting the characteristic of cluster 3 was found.

Those characteristic behaviors which cause children to be identified by their teachers as distractible or disorganized seem to be among the more prominent expressions of low level lead exposure. The significant differences on the G.F.W. selective attention test support this possibility. Longer reaction time under varying intervals of delay, another measure of disturbed attention, has also been shown (4). It is tempting to speculate that the midline slowing on the EEG reported here is an electrophysiological expression of the same process.

The lead-associated alterations reported here span the range from CNS electrophysiology, through speech processing to classroom behavior. The breadth of these effects and their intimate relation to functions critical to the child's ability to attend to stimuli and learn argue that at the exposure encountered here, lead has produced adverse health effects. Follow-up studies of these children will provide important information about the consequences of these alterations upon their academic and social adaptations.

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